REMARKS

The Pending Claims:

Claims 1-29, 31, 32, 34, 36, and 38-44 are pending. Claims 1-29, 31, 32, 34, 36 and 44 are under active consideration. Claims 38-43 are withdrawn from consideration. Claims 30, 33, 35 and 37 are canceled.

The Office Action:

Claims 1-38 and 44 are rejected.

Claim 30 is objected to.

The Amendment:

Claims 1, 34, 36, and 38 are currently amended. Claim 1 has been amended to include the limitations of claims 33 and 35. Claims 34, 36 and 38 have been amended to depend from claim 1, instead of canceled claim 33. The amendments are fully supported by the application as filed and do not add new matter.

In the Notice of Noncompliant amendment, the Examiner identified several typographical errors that were inconsistent with the previous versions of the claims. Notably, claim 24 included "GAP" which should have been GaP and "AIP", which should hve been AlP. Furthermore, directly following "substrate" in line 17 of claim 1, the period contained a strike-through, which would be more clear as a double bracket. Appropriate corrections have been made in the claims included herewith.

Amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicant expressly reserves the right to file one or more continuing applications hereof containing the canceled or unamended claims. Entry of the claim amendments is respectfully requested.

Summary of Examiner Interview:

A telephone interview was conducted on November 6, 2006. Participating in the interview were Examiner Robert Crow and Examiner Juliet Switzer of the United States

Patent and Trademark Office, and Applicant's representative, Joel Silver. Discussed during the interview were the rejections to claims 1, 12, 33 and 35.

Applicants proposed incorporating the limitations of claims 35 and/or 12 into claim 1 to overcome the outstanding rejections. Particularly, Applicants asserted that in view of the proposed amendment there was no reason to combine the cited references (Mirkin, Pinkel and Weiss), which would effectively render Mirkin inoperable for its cited purpose. The Examiner suggested that Applicants submit a written response, which has been done in the following section of this paper.

Applicants would like to sincerely thank Examiner Crow and Switzer for their time and efforts in discussing the issues presented in the Official Action.

RESPONSE TO REJECTIONS

Rejection under 35 U.S.C. § 112, Second Paragraph:

Claim 30 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Additionally, claim 30 is objected to for the alleged use of informalities. In view of the current amendment canceling claim 30, Applicants respectfully submit that the rejection has been rendered moot.

Rejection under 35 U.S.C. § 102(b):

Claims 1-5, 14-15, 17, 19, 24-25, 28, 30-32 and 44 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mirkin et al. (WO 98/04740). Claims 33 and 35 are not rejected under 35 U.S.C. § 102(b). In view of the current amendment which incorporates the limitations of claims 33 and 35 into claim 1, applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103(a):

I. Claims 1 and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Pearson et al. (U.S. Patent No. 5,916,779). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1 and dependent claim 6 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Pearson does not cure Mirkin's deficiencies and is only cited for description of reverse transciptase. Accordingly, withdrawal of the obviousness rejection to claims 1 and 6 in view of Mirkin and Pearson is respectfully requested.

II. Claims 1 and 7-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Fischer (U.S. Patent No. 5,876,932). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1, and therefore dependent claims 7-9 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Fischer does not cure Mirkin's deficiencies and is only cited for description of primers. Accordingly, withdrawal of the obviousness rejection to claims 1 and 6 in view of Mirkin and Pearson is respectfully requested.

III. Claim 10 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Fischer (U.S. Patent No. 5,876,932) and further in view of Anolles (U.S. Patent No. 5,962,221). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1 and therefore dependent claim 10 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Annolles and Fischer do not cure Mirkin's deficiencies and are only cited for description of particular primers. Accordingly, withdrawal of the obviousness rejection to claim 10 in view of Mirkin, Fischer and Anolles is respectfully requested.

IV. Claim 11 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Fischer (U.S. Patent No. 5,876,932) and further in view of Kambra et al. (U.S. Patent No. 5,985,556). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1 and therefore dependent claim 11 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Kambra and Fischer do not cure Mirkin's deficiencies and are only cited for description of particular primers.

Accordingly, withdrawal of the obviousness rejection to claim 11 in view of Mirkin, Fischer and Kambara is respectfully requested.

V. Claims 1 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Hunkapiller et al. (U.S. Patent No. 5,942,609). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1 and therefore dependent claim 12 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Hunkapiller does not cure Mirkin's deficiencies and is only cited for description of ligation on solid supports. Accordingly, withdrawal of the obviousness rejection to claim 1 and 12 in view of Mirkin and Hunkapiller is respectfully requested.

VI. Claims 1 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Agrawal et al. (U.S. Patent No. 5,652,103). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1 and therefore dependent claim 13 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Agrawal does not cure Mirkin's deficiencies and is only cited for description of terminal transferases. Accordingly, withdrawal of the obviousness rejection to claim 1 and 13 in view of Mirkin and Agrawal is respectfully requested.

VII. Claims 1 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Cheuziat et al. (U.S. Patent No. 5,849,547). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1 and therefore dependent claim 16 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Cleuziat does not cure Mirkin's

deficiencies and is only cited for description of hybridization to sequences containing modified bases. Accordingly, withdrawal of the obviousness rejection to claim 1 and 16 in view of Mirkin and Cleuziat is respectfully requested.

VIII. Claims 1 and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Klinger et al. (U.S. Patent No. 5,693,783). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1 and therefore dependent claim 18 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Klinger does not cure Mirkin's deficiencies and is only cited for description of hybridization to metaphase spreads of chromosomes. Accordingly, withdrawal of the obviousness rejection to claim 1 and 18 in view of Mirkin and Klinger is respectfully requested.

IX. Claims 1, 21, and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Lebo (U.S. Patent No. 5,665,540). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1 and therefore dependent claims 21 and 22 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Lebo does not cure Mirkin's deficiencies and is only cited for description of hybridization of probes to interphase nuvlei. Accordingly, withdrawal of the obviousness rejection to claim 1, 21 and 22 in view of Mirkin and Lebo is respectfully requested.

X. Claims 1, 23, and 27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Bruchez (Science vol. 281, pages 2013-2016 (1998)). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event." Page 20, last line. Claim 1 and therefore dependent

claims 23 and 27 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Bruchez is cited for description of core/shell nanocrystals and wherein the shell can be CdS. Accordingly, all of the limitations of the claims are not present in the cited art.

Furthermore, Mirkin's failure to describe a multiplex-type assay wherein multiple biding events are separately detectable is not simply an oversight; instead, it represents a fundamental difference between Mirkin's disclosure and the present claims.

Mirkin describes a nucleotide detection assay that relies on a detectable change "brought about as a result of the hybridization of oligonucleotides on the nanoparticles to the nucleic acid." *Abstract.* The detectable change as a result of nucleotide hybridization is axiomatic to Mirkin. Where fluorescent dyes are described, there is a donor-acceptor motif, wherein dye quenching ceases upon hybridization to the target sequence.

The present rejection is based on the amplification scheme described in Figure 13, which involves aggregation of gold nanoparticles through hybridizable binding sequences, forming a dendritic-like matrix which manifests itself as a "darkened area" on the substrate (see Example 6). The purpose of this scheme, as with all other schemes in Mirkin, is to induce a detectable change in the mixture upon hybridization of the nucleotide sequences (page 74). Mirkin does not describe the use varying nanoparticles and tag sequences in Figure 13, because that is contrary to the primary objective, which is to amplify a signal. The sequences simply provide a facet for such amplification.

Conversely, the tag sequences in the present claims are designed for selective binding of distinct nanocrystals, thereby permitting multiplexing. Accordingly, Mirkin, Bruchez and the present claims are at cross purposes, and modification of either would render the other inoperable for its designed purpose. Accordingly, withdrawal of the obviousness rejection to claim 1, 23 and 26-27 in view of Mirkin and Bruchez is respectfully requested.

XI. Claims 1 and 29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Kohne (U.S. Patent No. 5,612,183). In view of the amendment, Applicants respectfully believe that this rejection has been rendered moot.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event…" Page 20, last line. Claim 1 and therefore dependent claim 29 specify that binding of each of the different targets to its corresponding different probe polynucleotide can be separately determined. Kohne does not cure Mirkin's deficiencies and is only cited for description of quantitation of probe binding. Accordingly, withdrawal of the obviousness rejection to claim 1 29 in view of Mirkin and Kohne is respectfully requested.

XII. Claims 1, 33-34, and 36-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin in view of Pinkel (U.S. Patent No. 5,690,894). Additionally, claim 35 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Mirkin and Pinkel as applied to claim 33, and further in view of Weiss et al. (U.S. Patent No. 5,990,479). Although claims 33 and 35 are canceled by this amendment, the limitations therein are now included in claim 1. Accordingly, applicants address the rejections with respect to current claim 1.

According to the Office Action, "Mirkin et al does not teach separate determination of each binding event. However Pinkel et al teach a method of assaying samples for probes (e.g., using a biosensor array to detect nucleic acid binding complexes, Abstract) wherein each binding event is separately determined (e.g., simultaneous assaying of binding components of a test sample are done on by discretely detection at individual locations [i.e., bundles of fibers]; Abstract) with the added benefit that the discrete addressing assists in rapid sample identification (Abstract). It would therefore have been obvious… to have modified the method comprising the detection as taught by Mirkin et al with separately determined detection as taught by Pinkel et al with reasonable expectation of success." Applicants respectfully disagree.

As recognized by the Office Action, Mirkin fails to describe a multiplex-type assay wherein multiple biding events are separately detectable. This omission is not simply an oversight by Mirkin; instead, it represents a fundamental difference between Mirkin's disclosure and the present claims.

Mirkin describes a nucleotide detection assay that relies on a detectable change "brought about as a result of the hybridization of oligonucleotides on the nanoparticles to

the nucleic acid." *Abstract.* The detectable change as a result of nucleotide hybridization is axiomatic to Mirkin. Where fluorescent dyes are described, there is a donor-acceptor motif, wherein dye quenching ceases upon hybridization to the target sequence.

The present rejection is based on the amplification scheme described in Figure 13, which involves aggregation of gold nanoparticles through hybridizable binding sequences, forming a dendritic-like matrix which manifests itself as a "darkened area" on the substrate (see Example 6). The purpose of this scheme, as with all other schemes in Mirkin, is to induce a detectable change in the mixture upon hybridization of the nucleotide sequences (page 74). Mirkin does not describe the use varying nanoparticles and tag sequences in Figure 13, because that is contrary to the primary objective, which is to amplify a signal. The sequences simply provide a facet for such amplification.

Conversely, the tag sequences in the present claims are designed for selective binding of distinct nanocrystals, thereby permitting multiplexing. Accordingly, Mirkin and the present claims are at cross purposes, such that a modification of either would render the other inoperable for its designed purpose.

According to the M.P.E.P. § 2143.01(VI) "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." *Citing, In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Furthermore, "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The desirability of the Office Action's proposed modification is not recognized in the prior and is contrary to the purpose of Mirkin.

Accordingly, it would not have been obvious to combine multiplexing described in Weiss and Pinkel to the methods described in Mirkin. The only basis on which that argument can be founded involves hindsight reconstruction of the present claims.

In view of the foregoing Applicants respectfully request withdrawal of the current rejections over Mirkin in view of Weiss and Pinkel.

The interview summary points out that sandwich assays are well known and that other art teaching the proposed method with labels other than nanocrystals may exist and that there would be a strong motivation to use nanocrystals with those methods. In view of this suggestion, Applicants have not added any additional limitations or material to the original claims as filed, which have been examined. Accordingly, no additional rejections are believed to be necessitated by this amendment and all of the previous rejections have been addressed.

CONCLUSION

In view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent at (541) 335-0165.

Respectfully submitted,

Date: June 4, 2007

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